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COSTS OF HOSPITALIZATION FOR HEMATOPOIETIC CELL TRANSPLANTATION (HCT) IN THE UNITED STATES (U.S.): A PILOT STUDY USING A LARGE NATIONAL COMMERCIAL PAYOR DATABASE

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HCT is a resource-intense and expensive procedure. Single institution studies have described costs of HCT; however, costs from the national perspective are not well known. We used a large US commercial payor database (Thomson Reuters MarketScan) to assemble a cohort of patients who received HCT. The aim of our study was to evaluate the feasibility of using this database to investigate costs over the first 100 days after transplantation among adult and pediatric recipients of allogeneic and autologous transplantation. Here we present results for HCT hospitalization. MarketScan is a claims and encounters database that includes specific health services records for employees and their dependents in a selection of large employers, health plans and government organizations. Claims and encounter data are linked to detailed patient demographic and enrollment information across sites and types of providers. For our study, we used ICD-9 diagnosis and procedure codes to identify HCT recipients. We identified 3816 patients who received HCT from 2007 to 2009; these patients accounted for 4026 HCT hospitalizations. Among these, 41% were allogeneic HCT, 49% were autologous HCT, and the type of HCT was not specified in 9%. The most common indication for allogeneic HCT was acute myeloid leukemia (20%), and for autologous HCT multiple myeloma was most common (40%). The mean length of hospital stay was 30 (SD 20) days for allogeneic and 19 (SD 11) days for autologous HCT recipients. The mean age for allogeneic HCT recipients was 43 (SD 18) years, while it was 51 (SD 16) years for autologous HCT recipients ($P<0.01$). The mean costs of HCT hospitalizations was $196,307 for allogeneic and $96,153 for autologous HCT recipients. Our study highlights the feasibility of using the MarketScan commercial payor database to identify HCT recipients and to study costs of HCT in the U.S. Ongoing analyses will describe total inpatient and outpatient costs within the first 100 days of HCT and variations in these costs by age group and geographic region.

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NOROVIRUS GASTROENTERITIS – AN EMERGING PATHOGEN IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) RECIPIENTS

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Background: Norovirus (family of the Calciviridae) infection is a common cause of acute gastroenteritis, however, data on norovirus infection is limited in immunocompromised patients. Here we report our single center experience with norovirus infection in 12 pediatric HSCT patients.

Methods: Patient demographics and transplant characteristics are described in Table 1.

Table 1. Patient Demographics and Transplant Characteristics

Patient #	Sex/Age (years)	Diagnosis	Donor type	Type of conditioning	Concurrent GVHD		
					Gut	Skin	Liver
1	M/1.0	HLH	URD	RIC	+	+	-
2	F/1.6	SCID	URD	RIC	-	+	-
3	M/9.6	Autoimmune neutropenia	URD	RIC	-	-	-
4	M/0.5	HLH	MSD	RIC	-	-	-
5	M/22.1	MDS	MSD	MAC	-	-	-
6	F/2.1	Ligase IV deficiency	URD	RIC	-	-	-
7	M/0.7	WAS	UCB	MAC	-	+	-
8	M/18.2	XLP	URD	RIC	+	-	-
9	M/5.8	SCID	URD	RIC	-	+	-
10	F/11.4	CML	URD	MAC	-	-	-
11	F/8.2	FA	URD	MAC	-	+	-
12	M/1.7	HLH	URD	RIC	-	-	-

RIC: reduced-intensity conditioning, MAC: myeloablative conditioning; HLH: hemophagocytic lymphohistiocytosis; SCID: severe combined immunodeficiency; MDS; myelodysplastic syndrome; WAS: Wiskott-Aldrich syndrome; XLP: X-linked lymphoproliferative syndrome; CML: Chronic myelogenous leukemia; FA: Fanconi anemia; URD: unrelated donor; MSD: matched sibling donor; UCB: unrelated cord blood; GVHD: graft versus host disease

Results: Twelve patients presented between January 2009-September 2011, with diarrhea. Most patients (9/12) also had significant nausea and vomiting. At initial presentation, patients had diarrhea for a median of 31 days (range: 3-72) and nausea/vomiting for 5 days (range: 1-30). One or more complications such as hypotension, hypovolemic shock, protein losing enteropathy, pneumatosis intestinalis occured in 9 patients, with 3 requiring transfer to intensive care unit for the same. All 12 patients had positive stool PCR. Eight patients had prolonged PCR positivity for more than 3 months, and one of them had intermittent shedding. These patients also had a prolonged clinical course with persistent or intermittent diarrhea, abdominal discomfort, nausea and vomiting. In total, 11 patients had significant weight loss and required supplemental intravenous/enteral nutritional support. Five patients had C. difficile and 4 had stool adenovirus positivity around the time of norovirus infection, however, they remained symptomatic despite clearing C. difficile and adenovirus in stool, correlating with persistent positive norovirus PCRs. All 12 patients were treated with intravenous immunoglobulin (IVIG) and 4 patients with severe or chronic course received 14 day course of nitazoxinide. Three out of 4 responded in terms of improved/resolved symptoms. In patients treated only with IVIG support, 7/8 cleared acute symptoms, but only two who became PCR negative, clearly had resolution of symptoms. Remaining 5 although improved initially, continued to have low grade chronic symptoms correlating with their PCR positivity.

Conclusion: Norovirus can have a prolonged chronic or relapsing course with significant morbidity and potential mortality in children undergoing HSCT. Treatment with IVIG and/or nitazoxinide appears to be effective in shortening the duration of symptoms. In addition, in our small cohort, achievement of PCR negativity seems to correlate with resolution of illness. Prospective studies including large number of patients are warranted to better understand norovirus disease in HSCT setting.

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HUMAN BIOMARKER DISCOVERY AND PREDICTIVE MODELS OF DISEASE PROGRESSION AND RESPONSE TO THERAPY FOR IDIOPATHIC PNEUMONIA SYNDROME

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Idiopathic pneumonia syndrome (IPS) is a frequently fatal complication following allogeneic BMT (allo-BMT). Experimental models have demonstrated a critical role for TNFα in the development of IPS, but mechanisms responsible for human disease are poorly characterized. Using samples collected from a pilot trial using etanercept (Enbrel ®) for IPS, we performed two separate label-free, proteomics experiments utilizing liquid chromatography and mass spectrometry to define inflammatory pathways contributing to the clinical syndrome. Allo-BMT recipients without complications

served as controls. Using samples from over 20 patients in four groups, we first conducted a discovery study to identify peptide variables that were significant across disease development (control vs. IPS) and time (day 0 vs. day of Dx or day 14 for controls). This revealed a set of 81 IPS-associated proteins that were verified by a number of methods, analyzed by ingenuity pathway analysis (IPA) and mapped to relevant immune pathways. IPA underscored a significant contribution of the acute phase response (TNFα / IL-6) signaling pathway during disease progression and revealed striking similarities between inflammation engendered during IPS in humans and mice. In the second verification analysis, we used only samples collected on day 0 from a larger cohort of patients to identify proteins that were effective variables for patient stratification. Identified peptides were subjected to predictive model building using the Ishwaran & Rao approach, which identified a set of robust plasma proteomic markers that could 1) predict the development of IPS, and 2) identify individuals who would ultimately respond to etanercept therapy. Analysis also revealed a number of novel proteins including attractin, lumican and LBP (the expression of which was verified by ELISA) that were significant in the discovery analysis and classifiers for disease development and or response to therapy. In sum, data generated in this translational research endeavor confirm previous clinical and experimental observations, provide new insights into the pathophysiology of IPS and identify a set of robust markers predictive for disease progression and response to therapy. As anti-TNF therapies are being developed as treatment for GVHD and other immune-mediated disorders, these results uncover a set of robust markers for patient stratification as a basis for individualized therapy that is ripe for further development.

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CMX001 AS THERAPY FOR SEVERE ADENOVIRUS INFECTIONS IN IMMUNOCOMPROMISED PEDIATRIC PATIENTS: SINGLE EXPERIENCE IN 5 PATIENTS

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Background: Adenovirus infection is a serious and often fatal complication in immunocompromised patients. There are currently no FDA-approved therapies for adenovirus infection. Cidofovir has been reported to have variable efficacy in treating Adenovirus but is associated with significant toxicity, especially renal and possible marrow toxicity. CMX001 is an oral Lipid -Antiviral-Conjugate that generates high intracellular levels of the active cidofovir-diphosphate without evidence of cidofovir-like nephrotoxicity. CMX001 is under investigation for the prevention of adenovirus disease.

Methods: We report on 5 patients with adenovirus disease treated with CMX001. Data were available for > 4 weeks of treatment. The median age was 1.9 years (Range 1.5 -11.8). The preparative regimen for the transplant patients consisted of Alemtuzumab, Fludarabine and Melaphalan. The graft source was bone marrow. GVHD prophylaxis was cyclosporine and methylprednisolone. Virologic response (VR) was defined as 99% drop from baseline or undetectable adenovirus DNA by PCR in plasma. Patient characteristics are shown in Table 1.

Results: Adenovirus disease was diagnosed at a median of 38 days (range -7 to 300) after transplantation. All patients received intravenous cidofovir for a median of 27 days (range 22-47) prior to starting CMX001. Four of five patients (80%) had a > 1 log drop in viral load at the end of 1 week of therapy. VR was seen in all patients with a median time to achieve VR was 2 weeks (range 1-3). Four patients received doses exceeding those currently being studied. No adverse events felt to secondary to CMX001 were seen with the 4 mg/kg/ doses. Two patients developed diarrhea that was likely related to CMX001 therapy while receiving the 2 mg/kg/dose twice weekly. Both patients had resolution of the symptoms when CMX001 was stopped and were able to resume therapy without recurrence of symptoms. No other significant side effects were observed.

Discussion: Our data demonstrates that CMX001 has efficacy against adenoviral infections with a favorable safety profile. In this critically ill group of patients, morbidity was high which may reflect that CMX001 is an investigational medicine and was not used as first line therapy for adenoviral infections in our institution for these patients. Clinicians caring for immunocompromised individuals with adenovirus infections should consider early use of CMX001 for severe adenovirus infections.

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PREVALENCE OF VIRAL INFECTIONS IN CHILDREN UNDERGOING FIRST ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: TWO YEAR SINGLE CENTER EXPERIENCE

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Background: Viral infections are a major cause of morbidity and mortality in patients receiving allogenic hematopoietic stem cell transplantation (HSCT). With the introduction of newer conditioning regimens, increasing use of reduced intensity protocols and T cell depletion, the risk of post-transplant viral infections may be increasing and specific high risk groups may need to be identified as candidates for intensive viral monitoring and pre-emptive strategies. Here we report our experience of viral infections in children undergoing their first allogenic HSCT from January 2009-December 2010.

Methods: One hundred twenty four patients, median age 4.9 years (range: 0.2-25.4) were identified and charts retrospectively reviewed. Ninety-five patients underwent HSCT for non-malignant disease, 29 for malignant disease. Graft source was unrelated donor in 102 (82%) and matched related in 22 (18%). Stem cell source was bone marrow in 94 (76%), peripheral blood stem cells in 16 (13%) and cord blood in 14 (11%). Sixty-four patients (35 with non-malignant disease, 29 with malignant disease) received myeloablative conditioning regimens. Forty-six patients (all with non-malignant disease)

Table 1. Patient Characteristics

Patient	Diagnosis	Days post HSCT of ADV detection	Sites of ADV infection	Viral Load (copies/ml)	Dose of CMX001	Adverse Events	Current Status/Followup (months)
1	SCID	N/A	Blood and Stool	770 million	4 mg/kg/dose BIW	None	Died of Disseminated Aspergillosis infection
2	SCID due to RAG2 mutation	-7	Blood and Stool	1.2 million	4 mg/kg/dose BIW	None	Alive and Well/ 8 months
3	FHL	300	Blood, Stool and Nasal Secretions	32,000	1 dose of 4 mg/kg/dose BIW then 11 doses of 2 mg/kg/dose BIW	Diarrhea	Died of Progressive Bronchiolitis Obliterans
4	XLP/MDS	70	Blood and Stool	89,000	5 doses of 4 mg/kg/dose BIW then 32 doses of 2 mg/kg/dose BIW	Diarrhea	Alive and Well/7 months
5	XLP	5	Blood and Stool	102,000	2 mg/kg/dose BIW	None	Died of Pulmonary TMA

SCID: Severe Combined Immunodeficiency; FHL: Familial Hemophagocytic Lymphohistiocytosis; MDS: Myelodysplastic Syndrome; XLP: X-Linked Lymphoproliferative Disorder; BIW: twice a week; QW: weekly; TMA: Thrombotic Microangiopathy.